"A Phase I Study of Gene Therapy of Cystic Fibrosis Utilizing a Replication Deficient Recombinant Adenovirus Vector to Deliver the Cystic Fibrosis Transmembrane Conductance Regulator Gene to the Airways."

The purpose of this study is to evaluate the safety and efficacy of gene therapy of cystic fibrosis with a replication deficient ΔE1,ΔE3 deleted adenovirus that directs expression of the normal CFTR mRNA and CFTR protein in mammalian cells. The virus, Av1CF2 will be administered to the upper (nasal) and lower (lobar bronchial) respiratory tract of patients with cystic fibrosis. This protocol is designed to demonstrate 1) the expression of normal CFTR mRNA *in vivo*, 2) the synthesis of CFTR protein and 3) the correction of epithelial cell cAMP dependent Cl^- permeability associated with cystic fibrosis. Potential toxic effects of Av1CF2 will be monitored by measuring clinical, radiographic, physiologic and biochemical parameters. The "pharmacokinetics" or longevity of expression and ability to re-infect the respiratory tract with Av1CF2 will be determined. Systemic and local immunologic consequences of Av1CF2 infection, the time of viral survival, and the potential for recombination or complementation of the virus to produce a replicating virus will be monitored in assessing the safety of the Av1CF2 recombinant virus. The safety and potential risks of exposure of personnel and cohorts of the patients after Av1CF2 administration will be assessed.

Consenting male or female patients of age 18 or greater with FVC >40% and documented homozygote Δ508 genotype will be recruited from the Cystic Fibrosis Center at Children's Hospital Medical Center, Cincinnati. Patients will be admitted to the Research Center, Children's Hospital after undergoing a two week period of intensive pulmonary toilet including antibiotics, postural drainage, aerosols, mucolytics and/or DNAse therapy (pending FDA approval of DNAse). Pulmonary function tests will be evaluated pre and post "cleanout." Av1CF2 will then be administered to specific regions of the inferior nasal turbinate, each patient group receiving 5×10^7, 5×10^8 or 5×10^9 PFU to defined areas of the nasal epithelium. CFTR mRNA, CFTR protein and Cl^- permeability will be assessed in nasal epithelial cells. Three days later, the patient will receive the Av1CF2 in the bronchus of the right or left lower lobe on bronchoscopic examination. Patient groups will receive 10^{10}, 10^{11} or 10^{12} PFU per dose in the lung. Clinical, radiographic, physiologic and cellular evidence of efficacy and toxicity will be assessed post administration. Viral clearance and replication will be assessed and the patient discharged when clear of infectious AV_1CF virus. 7.5 weeks after initial treatment, the patient will be readmitted and the presence of CFTR mRNA and lung function re-assessed. The same dose of virus previously administered to a particular patient will then be readministered to evaluate the potential for reinfection and expression of the CFTR mRNA to the lung epithelium.

The virus, Av1CF2, was constructed by Bruce Trapnell at Genetic Therapy, Inc., Gaithersberg, Maryland, from genetic material obtained from the adenovirus serotype 5. In Av1CF2, human CFTR mRNA is driven by the RSV, (Rous sarcoma promoter-enhancer) and terminates with SV40 poly A signals. The virus harbors deletions in the E1 (Δ E1) and E3 regions (Δ E3) deleted to block replication and to provide insert space for the incoming cDNA respectively. Similar adenoviral constructs have been used to transfer cDNA's for a variety of genes to various mammalian cells in vitro and to lung epithelial tissues *in vivo* by this laboratory and by others. It is hoped that these studies will demonstrate the biologic expression *in vivo* and safety of the Av1CF2 vector as a phase I study and support the long term goal of CFTR gene transfer that will lead to physiologically, and ultimately clinically, relevant reconstitution of the abnormalities that cause pulmonary disease in cystic fibrosis.